REMARKS

The Invention.

The present invention provides a novel β-glucosidase nucleic acid sequence, designated *bgl5*, and the corresponding BGL5 amino acid sequence. The presently claimed invention also provides expression vectors and host cells comprising a nucleic acid sequence encoding BGL5, recombinant BGL5 proteins and methods for producing the same.

Status of the Application.

Claims 1-17, 19-20, 22-24 and 26 are pending in the application. Claim 1 has been cancelled herein. Claims 2, 6 and 8 have been amended herein. Claims 2 and 8 were amended to clarify what Applicants believe is the mete and bounds of the invention. Claim 6 was amended to recite the correct dependency. Support for these amendments may be found throughout the specification as filed. No new matter is introduced by these amendments and their entry is respectfully requested.

35 U.S.C. §112, first paragraph.

Claims 1-17, 19-20, 22 and 26

Claims 1-17, 19-20, 22 and 26 stand rejected under 35 USC §112, first paragraph as failing to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Specifically, the Examiner assert that the claims are so broad as to encompass any polynucleotide from any source encoding an endoglucanase, vectors, host cells, and method or expressing said endoglucanase and a host cell expressing an inactivated endoglucanase. Applicants respectfully traverse.

In the present case, the Office Action provides no extrinsic evidence regarding non-enablement. Instead, the Office Action relies upon the opinion of the Examiner that the breadth of the claim is unsupportable because it is asserted that "one of ordinary skill in the art would be reduced to ... undue experimentation." The Office Action is lacks technical reasoning and/or reference to extrinsic evidence which supports the

position therein that one of skill in the art would be unable to make and use the invention as claimed. Accordingly, Applicants respectfully submit that the unsupported opinion of the Examiner that a specific claimed embodiment is "too broad" is not the standard of non-enablement.

The fact that experimentation may be complex does not necessarily make it undue, if the art engages in such experimentation (MPEP 2164.01 and cites therein). Applicants submit that more than sufficient teaching is provided as to how to make and use the present invention. Indeed, as the MPEP states at 2164.01(b):

> As long as the specification discloses at least one method for making and using the claimed invention that bears reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Failure to disclose other methods by which the claimed invention may be made does not render a claim invalid under 35 U.S.C. 112. *Spectra-Physics, Inc. v. Coherent, Inc*, 827 F.2d 1524, 1533, 3 USPQ2d 1737, 1743 (Fed. Cir.), *cert. denied*, 484 U.S. 954 (1987).

Thus, the fact that Applicants do not explicitly provide examples regarding every polynucleotide encompassed by the present invention does not render the present claims unpatentable. Indeed, "a patent need not teach, and preferably omits what is well known in the art" (*See e.g., In re Buchner*, 929 F.2d 660, 661; MPEP 2164.01).

It was well known in the art at the time of filing that certain motifs defined the characteristics of the enzyme. In the present case, the β–glucosidase belongs to family 1 (see page 22, first full paragraph). Indeed, two such conserved regions are identified in Takashima et al. (J. Biochem (1999) 125:728-736; Figure 3). Alignment of family members and modifying non-conserved regions was also well-known in the art at the time of filing. See, for example, page 21, lines 16-27.

Numerous specific strategies for modifying proteins are known in the art. For example, Additional stability of may be introduced by the introduction of proline residues (*see, e.g.,* Watanabe, *et al., Eur. J. Biochem.* 226:277-283 (1994)). Similarly, glycine residues have no β-carbon, and thus have considerably greater backbone conformational freedom than many other residues. Replacement of glycines, preferably

with alanines, may reduce the entropy of unfolding and improve stability (*see, e.g.*, Matthews, *et al.*, *Proc. Natl. Acad. Sci. USA* 84; 6663-6667 (1987)). Additionally, by shortening external loops it may be possible to improve stability. It has been observed that hyperthermophile produced proteins have shorter external loops than their mesophilic homologues (*see, e.g.*, Russel, *et al., Current Opinions in Biotechnology* 6:370-374 (1995)). The introduction of disulfide bonds may also be effective to stabilize distinct tertiary structures in relation to each other. Thus, the introduction of cysteines at residues accessible to existing cysteines or the introduction of pairs of cysteines that could form disulfide bonds would alter the stability of a beta-glucosidase variant.

Similarly, decreasing internal cavities by increasing side-chain hydrophobicity may alter the stability of an enzyme. Reducing the number and volume of internal cavities increases the stability of enzyme by maximizing hydrophobic interactions and reducing packing defects (*see, e.g.*, Matthews, *Ann. Rev. Biochem.* 62:139-160 (1993); Burley, *et al., Science* 229:23-29 (1985); Zuber, *Biophys. Chem.* 29:171-179 (1988); Kellis, *et al., Nature* 333:784-786 (1988)). Modification by substitution to alanine or proline may increase side-chain size with resultant reduction in cavities, better packing and increased hydrophobicity. Substitutions to reduce the size of the cavity, increase hydrophobicity and improve the complementarity the interfaces between the domains of beta-glucosidase may improve stability of the enzyme. Specifically, modification of the specific residue at these positions with a different residue selected from any of phenylalanine, tryptophan, tyrosine, leucine and isoleucine may improve performance.

Other possible alterations are referred to in, *e.g.*, Eriksson, *et al., Science* 255:178-183 (1992)) and Tanner, *et al., Biochemistry* 35:2597-2609 (1996)). All of these techniques were well known and understood in the art at the time of filing and therefore did not need to be included in the specification.

With regard to structure/function, Applicants have provided in claim 2 a recitation of a structure, e.g., the presence of a nucleotide encoding an amino acid sequence as shown in SEQ ID NO:2, and a function, i.e., beta-glucosidase activity, as measured using standard enzyme activity assays. See page 11, first full paragraph.

Furthermore, Applicant has provided methods of preparing and using the polynucleotides. See page 18 *et seq*. This would not involve undue experimentation, but would be routine to one of ordinary skill in the art. Applicant asserts that they have provided written description of their invention and have provided ample exemplification, given the state of the art, to allow one of skill in the art to make and use the invention without undue experimentation. Applicants assert that the claims are enabled.

Thus, the one skilled in the art would compare the beta-glucosidase with at least one homologue and the select amino acids from the homologue(s) that are different from the beta-glucosidase to prepare a variant beta-glucosidase, as determined based on protein function (*i..e*, the differing amino acids of the homologue(s) are incorporated into the sequence of the first protein in order to produce a variant protein), as determined using standard enzyme activity assays; (see page 11, first full paragraph, and throughout the Specification). Applicants submit that the Specification provides what is needed so that use of the methods is well within the skill of those in the art. Indeed, because the making and using other improved proteins are within the skill of those in the art utilizing the claimed methods, the Claims are enabled. Thus, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. §112, second paragraph.

Claim 8

Claim 8 and claims 9 and 11 dependent therefrom stand rejected under 35 USC §112, second paragraph as being indefinite. Specifically, the Examiner asserts that Applicants are "directly comparing the claimed nucleic acid with an amino acid sequence" which requires correction. Applicants have corrected the error rendering this rejection moot. Withdrawal is respectfully requested.

35 U.S.C. §102(b).

Claims 1 and 6-7 stand rejected under 35 USC §102(b) as being anticipated by Takashima et al (J. Biochem (1999) 125:728-736). Specifically, the Examiner asserts

that Takashima et al. discloses all elements of the claimed invention within its four corners. Applicants respectfully traverse.

Applicants have cancelled claim 1 and corrected the dependency of claim 6. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the above amendments, as well as the remarks, the Applicants believe the pending claims are in condition for allowance and issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (650) 846-7615.

Respectfully submitted,

Victoria L. Boyd

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Victoria L. Boyd
Registration No. 43,510

Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304
Tel: 650-846-7615
Fax: 650-845-6504